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Understanding the molecular basis of nicotine addiction by integrative genomic analyses in a rat model and hiPSC-derived DA neurons

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Cigarette smoking is the largest preventable risk factor for mortality. NIC sensitization (SST) and self-administration (SA) in rats correlate with a number of neurobiological changes; however, the molecular basis of these changes has yet to be determined. We aim to identify translatome profiles (RNA transcripts bound to ribosomes and actively involved in protein synthesis) in NIC addiction-relevant brain regions following NIC sensitization and compare to NIC-treated dopaminergic (DA) neurons of human induced pluripotent stem cells (hiPSCs). With the F1 F344/BN hybrid rats, we found that both male and female F1s show a dose-dependent increase in NIC-induced locomotion; however, only males exhibited NIC sensitization. For hiPSC-DA neurons as a model, we evaluated the transcriptomic similarity of the hiPSC-DA neurons to human postmortem brains relevant to addiction and found a strong expression correlation between the two. We thus subjected DA neurons to NIC treatment and recorded neuron firing by multi-electrode analysis (MEA). We observed robust DA neuron firing; although NIC did not show significant effect on neuronal activity, which is likely due to the receptor desensitization. We are performing translatome profiling for F1 rats in major brain regions relevant to NIC addiction as well as for NIC-treated DA neurons. Pilot results showed that the sequencing reads around the start codon ATG formed an expected pattern of ribosome footprints in active protein translation. Identifying novel gene targets relevant to NIC sensitization will increase understanding of the neurobiology of human NIC abuse and inform the development of more effective therapeutics.